

19



Europäisches Patentamt
European Patent Office
Office européen des brevets

11 Publication number:

**0 241 201
A2**

12

EUROPEAN PATENT APPLICATION

21 Application number: 87302769.2

51 Int. Cl.4: A61K 37/64

22 Date of filing: 31.03.87

30 Priority: 07.04.86 US 848528

43 Date of publication of application:
14.10.87 Bulletin 87/42

84 Designated Contracting States:
AT BE CH DE ES FR GB IT LI LU NL SE

71 Applicant: MERCK & CO. INC.
126, East Lincoln Avenue P.O. Box 2000
Rahway New Jersey 07065-0900(US)

72 Inventor: Sweet, Charles S.
741 Cowpath Road
Telford Pennsylvania 18969(US)

74 Representative: Hesketh, Alan, Dr.
European Patent Department Merck & Co.,
Inc. Terlings Park Eastwick Road
Harlow Essex, CM20 2QR(GB)

54 Angiotensin converting enzyme inhibitors useful in prolonging survival of mammals with congestive heart failure.

57 Angiotensin converting enzyme (ACE) inhibitors have been found useful in prolonging the survival rate of mammals with congestive heart failure (CHF), particularly those who had a large infarct.

EP 0 241 201 A2

ANGIOTENSIN CONVERTING ENZYME INHIBITORS USEFUL IN PROLONGING SURVIVAL OF MAMMALIANS WITH CONGESTIVE HEART FAILURE

BACKGROUND OF THE INVENTION

The use of the angiotensin converting enzyme (ACE) inhibitor captopril to prolong survival of congestive heart failure (CHF) rats has been evaluated by M.A. Pfeffer, et al. [*Circulation*, 72, No. 2, 406-412 (1985)]. This study reports that CHF rats having small infarcts (5%-49.99%) and moderate infarcts (20%-39.9%) which were treated with captopril demonstrated reduced mortality, but that a long term beneficial effect was not sustained with captopril in CHF rats having large infarcts (40%). From this study, it appears that survival of rats with small infarcts after one year was about 70%; survival of rats with moderate infarcts after one year was about 50%; and, survival of rats with large infarcts after one year was about 18%.

SUMMARY OF THE INVENTION

It has now been found that treating CHF rats having large infarcts with enalapril, enalaprilat, or lisinopril significantly prolongs their survival.

Enalapril, enalaprilat, lisinopril, and related carboxyalkyl dipeptide derivatives as well as methods for their preparation are disclosed in U.S. Patents 4,374,829 and 4,472,380 which are incorporated herein by reference. Enalapril is the chemical compound N-[(1S)-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline; enalaprilat is the chemical compound N-[(1S)-carboxy-3-phenylpropyl]-L-alanyl-L-proline; and, lisinopril is the chemical compound Na-[(1S)-carboxy-3-phenylpropyl]-L-lysyl-L-proline.

DETAILED DESCRIPTION OF THE INVENTION

ASSAY METHOD

PROTOCOL

Commercially obtained male Sprague-Dawley rats ranging in age from 16 to 20 weeks, were housed in our animal facility for at least 2 weeks before operation. The intramyocardial artery was ligated (or a sham operation) was performed in each by a well-known method. Ten (10) days after the operative procedure all survivors were briefly anesthetized with ether and electrocardiograms were obtained. At the time of anesthesia, each rat was identified and a balanced-block randomization process was used to allocate animals to either tap

water or enalapril (in drinking water) therapy groups. This randomization process was stratified according to three arbitrary electrocardiographic groups. The first group had a normal QRS complex without evidence of a pathologic Q wave in limb leads I or aVL; the second group had a Q wave (<1 mV) in either of leads I or aVL, yet maintained a precordial R wave total of 10 mV or greater; and the third group had both abnormal limb-lead Q waves and a sum of precordial R waves that was 10 mV or less. This electrocardiographic classification system was used only to maintain a balance of rats with and without infarction in the placebo and enalapril groups, not for the subsequent survival analysis, which was performed with the histologic determinations of the size of myocardial infarction only.

Animals (2-3) were housed in clear polyethylene cages (up to a maximum of four rats per cage) and placed according to therapy assignment and time of entry into the study. Twenty-five animals were allowed free access to food and the assigned therapy (water or enalapril, 4.0 mg/kg/day in the drinking water). The room was temperature and humidity controlled and had a 12 hour light-dark cycle. The cages were maintained on two racks, each of which abutted one side of a double-sided laminar flow unit (Germ Free Laboratories). Cages with animals assigned to tap water or enalapril were placed on the rack. An additional 50 rats with the sham operation were selected from the same group used for this study and maintained concurrently with the study animals. Twenty-five received tap water and twenty-five received enalapril. Each animal was followed until death or for up to 1 year after the operative procedure.

Cages were inspected for dead animals daily on weekdays, weekends and holidays. The date of each death was noted and the carcass was weighed and a gross post-mortem examination was performed on many of the rats. The heart was removed and placed in formalin. All survivors at 1 year after infarction were anesthetized with ether and the heart of each was arrested with intravenous KCl. Blood samples were also taken from the survivors to determine drug and ACE inhibitor levels.

PATHOLOGY

The formalin-fixed heart was examined for infarcted areas. The atria and great vessels were trimmed from the ventricles. In most experiments, the right ventricular free wall was dissected from

the left ventricle and both ventricles were weighed separately. The left ventricle was dehydrated in alcohol, cleared in xylene and embedded in paraffin. Transverse 50 mm sections were cut from the apex to the base of the left ventricle. Several sections were mounted and stained with Masson's trichrome from which hematoxylin was omitted to provide a clearer discrimination between fibrous scar and muscle.

A slide of each section then was projected onto a screen for the planimetric measurement (Zeiss videoplan) of size of infarction. The endocardial and epicardial circumferences as well as the lengths of scar for each of these surfaces were measured for each section. The lengths of scar and of circumference were summed separately for each of the epicardial and endocardial surfaces and the sums were expressed as a ratio of scar length to ventricular circumference for each surface. These two ratios were then averaged and expressed as a percentage to define size of infarction. Since serial sections of the entire left ventricle were evaluated, the size of infarction determined represents the percent of the left ventricular endocardial and epicardial surface areas occupied by fibrous scar tissue.

ANALYSIS

Comparisons of survival in untreated and enalapril treated rats were performed separately by log-rank tests for all of the rats with and without infarction. No analyses were performed in the two groups based on size of infarction.

RESULTS

The results obtained for rats with large infarcts; i.e., $\geq 40\%$, are set forth in Figure 1. As shown in Figure 1, about 25% of rats having large infarcts survived for 1 year upon being treated with 1 mg/kg/day of enalapril. As noted earlier, the one year survival of rats with large infarcts after treatment with about 200 mg/kg/day of captopril was about 18%. Thus, use of enalapril at substantially lower doses than captopril results in prolonging CHF survival by about 50% more than captopril. More significantly, these results indicate enalapril is an effective therapeutic agent in prolonging survival of CHF mammals, particularly those who have experienced large infarcts and that similar benefits would be expected by treating humans affected with CHF.

Claims

1. The use of an angiotensin converting enzyme inhibitor selected from the group consisting of enalapril, enalaprilat and lisinopril, for the manufacture of a medicament useful for prolonging survival of mammals with congestive heart failure.

2. The use as claimed in Claim 1 wherein the congestive heart failure is an infarct $\geq 40\%$.

3. The use as claimed in Claim 1 wherein the angiotensin converting enzyme is enalapril.

4. The use of an angiotensin converting enzyme selected from the group consisting of enalapril, enalaprilat and lisinopril, for the manufacture of a medicament useful for prolonging survival of mammals with congestive heart failure having an infarct $\geq 40\%$.

5. The use as claimed in Claim 4 wherein the angiotensin converting enzyme is enalapril.

FIG 1

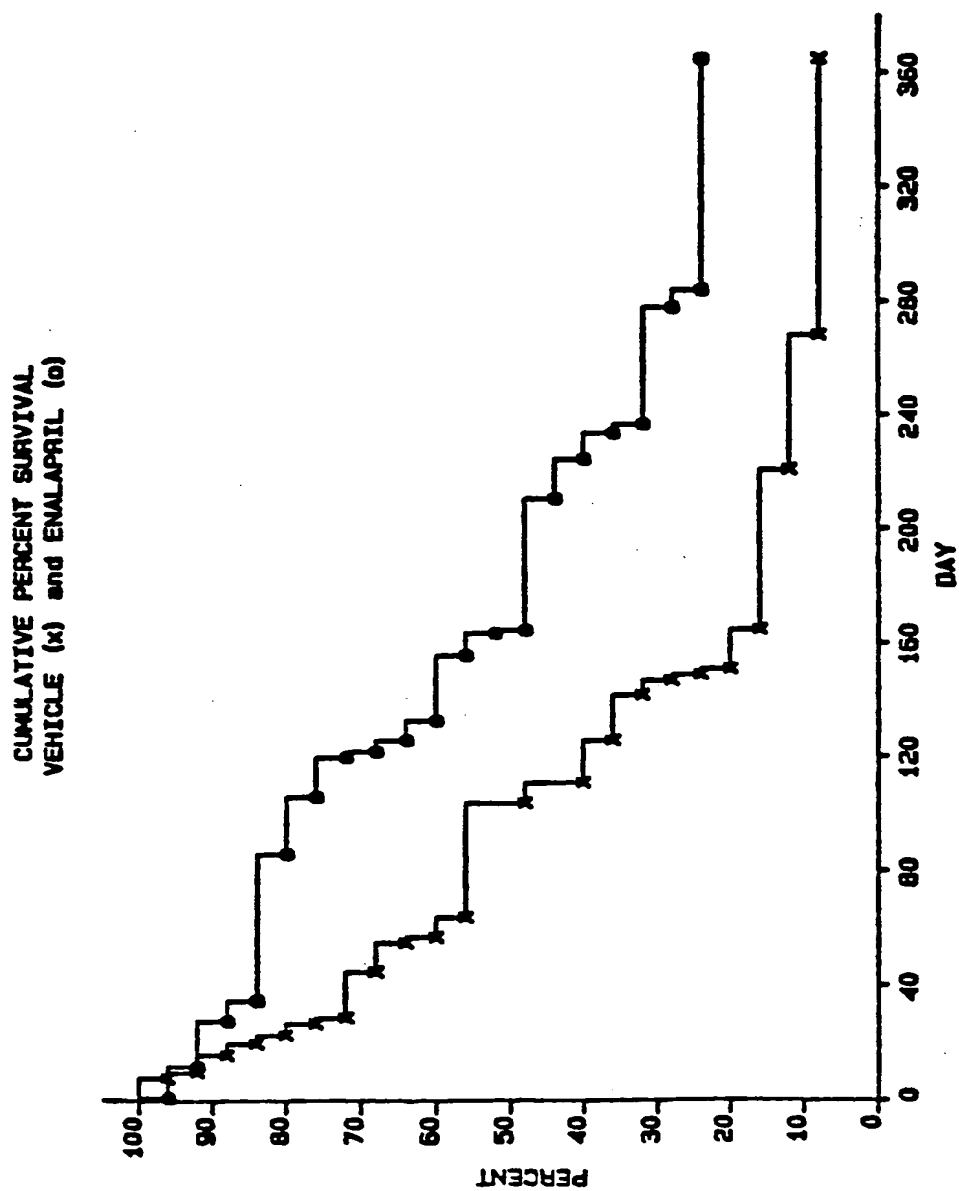
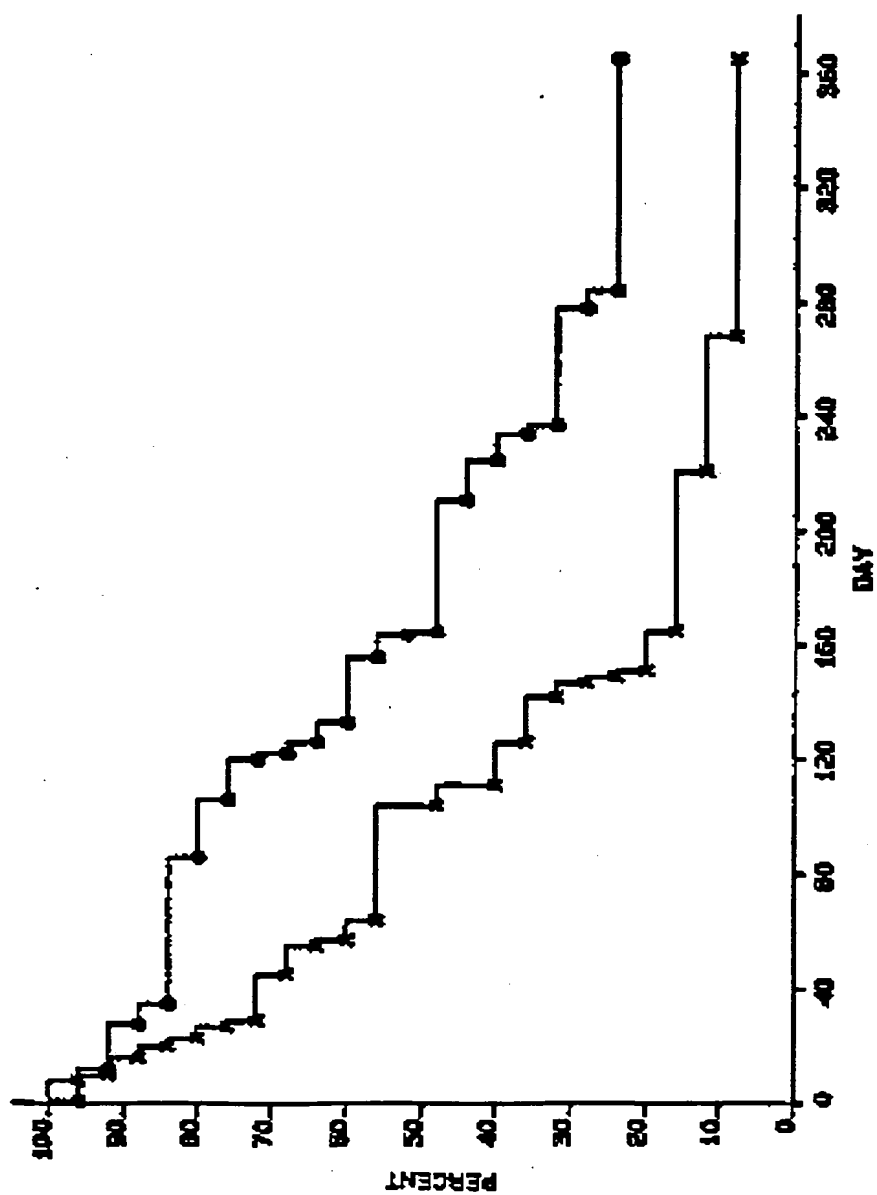


FIG 1

CUMULATIVE PERCENT SURVIVAL
VEHICLE (x) and ENLAPHEIL (o)



⑫ **EUROPEAN PATENT APPLICATION**

⑰ Application number: 87302769.2

⑨ Int. Cl.⁵: **A61K 37/64**

⑳ Date of filing: **31.03.87**

③① Priority: **07.04.86 US 848528**

③② Date of publication of application:
14.10.87 Bulletin 87/42

③③ Designated Contracting States:
AT BE CH DE ES FR GB IT LI LU NL SE

③④ Date of deferred publication of the search report:
23.05.90 Bulletin 90/21

⑦① Applicant: **MERCK & CO. INC.**
126, East Lincoln Avenue P.O. Box 2000
Rahway New Jersey 07065-0900(US)

⑦② Inventor: **Sweet, Charles S.**
741 Cowpath Road
Telford Pennsylvania 18969(US)

⑦③ Representative: **Hesketh, Alan, Dr.**
European Patent Department Merck & Co.,
Inc. Terlings Park Eastwick Road
Harlow Essex, CM20 2QR(GB)

⑤④ **Angiotensin converting enzyme inhibitors useful in prolonging survival of mammals with congestive heart failure.**

⑤⑦ **Angiotensin converting enzyme (ACE) inhibitors have been found useful in prolonging the survival rate of mammals with congestive heart failure (CHF), particularly those who had a large infarct.**

EP 0 241 201 A3



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT
which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

Application number

EP 87 30 2769

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	THE MEDICAL JOURNAL OF AUSTRALIA, vol. 141, no. 11, November 24, 1984, Glebe, AU; G. JENNINGS et al.: "Enalapril for severe congestive heart failure" * Abstract; results; discussion *	1-5	A 61 K 37/64
X	AMERICAN HEART JOURNAL, vol. 109, no. 2, February 1985, pages 222- 228, St. Louis, US; C.E. HOCK et al.: "Preservation of ischemic myocardium by a new converting enzyme inhibitor, enalaprilic acid, in acute myocar- dial infarction" * Abstract *	1-5	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			A 61 K 37/00
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: Claims searched incompletely: 1 Claims not searched: Reason for the limitation of the search:</p> <p>See sheet -B-</p>			
Place of search THE HAGUE		Date of completion of the search 26-02-1990	Examiner DULLAART
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO Form 1505.1 03/82



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	BR. HEART J., vol. 54, 1985, pages 405-414, London, GB; B.P. McGRATH et al.: "Controlled trial of enalapril in congestive cardiac failure" * Abstract; page 412, column 2 * --	1-5	
X	ANNALS OF CLINICAL RESEARCH, vol. 18, February 1986, pages 124-128, Helsinki, FI; J. REMES et al.: "Enalapril in chronic heart failure, a double-blind placebo-controlled study" * Abstract; results; discussion * --	1-5	TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
X	AM. J. CARDIOL., vol. 57, no. 6, February 1986, pages 459-462, New York, US; E.P. KROMER et al.: "Effectiveness of converting enzyme inhibition (enalapril) for mild congestive heart failure" * Abstract; results; discussion * --	1-5	
X	PHARMACOLOGY, vol. 29, 1984, pages 61-69, Karger AG, Basel, CH; A.M. LEFER et al.: "Cardioprotective effects of enalapril in acute myocardial ischemia" * Abstract * --	1-5	
X	LA PRESSE MEDICALE, vol. 14, no. 44, December 19, 1985, pages 2215-2217, Masson, Paris, FR; J.P. BOUNHOURE: "Traitement de l'insuffisance cardiaque par l'énalapril" * Abstract * -----	1-5	



EP 87 30 2769

Sheet -B-

MEANINGFUL SEARCH NOT POSSIBLE OR INCOMPLETE SEARCH

In most scientific literature, no percentage of infarct in congestive heart failure (CHF) is given. Therefor, the infarct of at least 40% was understood as severe congestive heart failure.

No pharmacological data is given for the use of lisinopril in severe CHF. Since the use of captopril, an other ACE-inhibitor, in severe CHF is limited (see page 1 of this application), it is very doubtful whether lisinopril has the same effects as enalapril. See Art. 84 EPC.

Claims 3-5 were understood for the use of an angiotensin converting enzyme inhibitor, which is enalapril or enalaprilat.